A genome wide survey supports the involvement of large copy number variants in mental retardation and comorbid psychiatric disorders

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Abstract

Copy Number Variants (CNVs) play a role in mental retardation and neuropsychiatric disorders. The aim of this study is to investigate the contribution of large CNVs to mental retardation (MR) and to report on CNV burden in MR with and without comorbid schizophrenia (SCZ). Subjects with MR+SCZ showed significantly more large (>1Mb) duplications compared to subjects with MR only. We replicated the role of CNVs in regions 1q21.1, 15q13.1, 16p13.1, and 22q11.21 in causing mental retardation with or without psychiatric comorbidity.

Background and aims

CNVs play a role in mental retardation and neuropsychiatric disorders (e.g., schizophrenia and autism). Consistent with high rates of comorbid diagnoses, a large overlap in the specific CNVs that play a role has been reported. The aims of this study are: i) to examine the contribution of very large (>1Mb) CNVs in the total mental retardation sample (N=170); ii) to compare the global CNV burden between 64 subjects with mental retardation and schizophrenia ("MR+SCZ") and 65 subjects with mental retardation and no comorbid psychiatric diagnosis except depression ("MR only"); iii) to assess the CNV rates in 12 candidate regions for neurodevelopmental disorders.

Methods

Patients were over 18 years of age, with an IQ of <70 and were recruited from the inpatient and outpatient services for Adults with Learning Disability (MR) of SE Scotland Health Boards. Mental health diagnoses were reached according to DSM-IV criteria using a semi structured interview.Genotype data were available from 182 subjects. The final sample after excluding subjects based on quality control criteria comprised 170 subjects. A comorbid diagnosis of major psychiatric illness was present in 100 subjects: schizophrenia (N=64), bipolar disorder (N=21), major depressive disorder (N=15); and 19 subjects were diagnosed with autism. Samples were genotyped on three plates by the Broad Institute using the Affymetrix 6.0 array which includes 906,600 SNP and 940,000 copy number probes. CNVs were called using Birdseye.

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Results

Including all CNVs larger than 100kb, CNV burden (total, deletions, and duplications) was similar in "MR+SCZ" and "MR only". Restricting analysis to CNVs larger than 1Mb, total CNV burden was higher in "MR+SCZ" (rate=.25) compared to "MR only" (rate=.09; empirical p=.03). Seven of the 33 large CNVs were located at candidate regions 1q21.1, 15q13.1, 16p13.1, and 22q11.21 which is a significant enrichment of the candidate regions (p=.002).

Table 1 Overview of CNV data (>100kb) in 170 subjects with mental retardation (MR) and a comparison by schizophrenia status

	Total MR (N=170)	MR +SCZ (N=64)	MR only (N=66)	Empirical p
N (rate)Total CNV	1791 (10.5)	663 (10.4)	678 (10.3)	.92
N (rate) Deletions	780 (4.6)	281 (4.4)	316 (4.8)	.49
N (rate) Duplications	1011 (5.9)	382 (6.0)	362 (5.5)	.44

Table 2 Overview of CNV data (>1Mb) in 170 subjects with mental retardation (MR) and a comparison by schizophrenia status

	Total MR (N=170)	MR +SCZ (N=64)	MR only (N=66)	Empirical p
N (rate) Total CNV	33 (.19)	16 (.25)	6 (.09)	.03
N (rate) Deletions	15 (.09)	6 (.09)	5 (.08)	.47
N (rate) Duplications	18 (.11)	10 (.16)	1 (.02)	.01

Conclusion

Candidate regions for neurodevelopmental disorders are significantly enriched with the large CNVs detected in this study. Furthermore, the CNV burden for large (>1Mb) CNVs is increased in patients with mental retardation and comorbid schizophrenia compared to patients with mental retardation only. We replicated the role of CNVs in regions 1q21.1, 15q13.1, 16p13.1, and 22q11.21 in causing mental retardation with or without psychiatric comorbidity.

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